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Abstract: Background Treatment with immune checkpoint and BRAF/MEK inhibitors has significantly improved the survival of patients with advanced cutaneous melanoma and other metastatic malignancies. Therapy-related uveitis is a rare ocular adverse event, which may potentially lead to legal blindness. The epidemiology of treatment-related uveitis is currently insufficiently known. Patients and methods In this cohort study, we asked whether exposure to either immune checkpoint or BRAF/MEK inhibitors was associated with a higher risk of developing uveitis compared with the general population. Based on a Bayesian framework, we estimated the probability of developing uveitis with a right-censored, exponential survival model using data from the Zurich Melanoma Registry. The registry included all adult patients treated for advanced cutaneous melanoma between January 2008 and December 2018 at the University Hospital of Zurich, Switzerland. Results In total, 304 patients (64%) were treated with immune checkpoint and 186 patients (38%) with BRAF/MEK inhibitors. Median follow-up time was 74 days (interquartile range: 57–233 days). Eleven patients developed uveitis and 30 patients died. We estimated the probability of developing uveitis per year in the general population as 0.05% (95% credibility interval [CrI]: 0.02%–0.1%). Corresponding posterior probabilities of treatment-related uveitis were 3.48% (95% CrI: 0.93%–7.49%) and 5.04% (95% CrI: 2.07%–9.19%) for immune checkpoint or BRAF/MEK inhibitors (posterior probability for difference: 76%). Conclusions Immune checkpoint and particularly BRAF/MEK inhibitor therapies are associated with an increase in the risk of developing uveitis. Treatment-related uveitis is not associated with systemic adverse events of immune checkpoint or BRAF/MEK inhibitors.

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Original Research

The association between immune checkpoint or BRAF/MEK inhibitor therapy and uveitis in patients with advanced cutaneous melanoma



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Abstract Background: Treatment with immune checkpoint and BRAF/MEK inhibitors has significantly improved the survival of patients with advanced cutaneous melanoma and other metastatic malignancies. Therapy-related uveitis is a rare ocular adverse event, which may potentially lead to legal blindness. The epidemiology of treatment-related uveitis is currently insufficiently known.

Patients and methods: In this cohort study, we asked whether exposure to either immune checkpoint or BRAF/MEK inhibitors was associated with a higher risk of developing uveitis compared with the general population. Based on a Bayesian framework, we estimated the probability of developing uveitis with a right-censored, exponential survival model using data from the Zurich Melanoma Registry. The registry included all adult patients treated for advanced cutaneous melanoma between January 2008 and December 2018 at the University Hospital of Zurich, Switzerland.

Results: In total, 304 patients (64%) were treated with immune checkpoint and 186 patients (38%) with BRAF/MEK inhibitors. Median follow-up time was 74 days (interquartile range: 57–233 days). Eleven patients developed uveitis and 30 patients died. We estimated the probability of developing uveitis per year in the general population as 0.05% (95% credibility interval [CrI]: 0.02%–0.1%). Corresponding posterior probabilities of treatment-related uveitis

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were 3.48% (95% CrI: 0.93%–7.49%) and 5.04% (95% CrI: 2.07%–9.19%) for immune checkpoint or BRAF/MEK inhibitors (posterior probability for difference: 76%).

Conclusions: Immune checkpoint and particularly BRAF/MEK inhibitor therapies are associated with an increase in the risk of developing uveitis. Treatment-related uveitis is not associated with systemic adverse events of immune checkpoint or BRAF/MEK inhibitors.

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1. Introduction

Treatment with immune checkpoint and BRAF/MEK inhibitors has significantly improved the survival of patients with advanced cutaneous melanoma [1–7]. These treatments have also been associated with a wide spectrum of autoimmune or inflammatory side-effects [8–11]. Some of the side-effects, such as cardiac or neurological events, occur very rarely but may potentially lead to irreversible organ damage [12]. Various studies have reported unspecific ocular adverse events occurring in about 1–4% of patients during treatment with immune checkpoint inhibitors [11,13–17] and in 25–100% of the patients treated with BRAF/MEK inhibitors [18–20]. Most of these ocular adverse effects, such as dry eye, ocular and orbital inflammations, neuro-ophthalmic disorders, or serous retinopathy, are reversible [21]. However, treatment-related uveitis—a rare but severe form of non-infectious inflammation of the uveal tract—can lead to irreversible visual impairment.

At present, only sparse data—mainly case reports—were describing uveitis as a potentially treatment-related side-effect [17,22–25]. Clinical trials, investigating treatment efficacy of immune checkpoint and BRAF/MEK inhibitors, have limited power to detect rare but potentially serious adverse events; hence, rare adverse events—such as uveitis—were systematically underreported [26]. The epidemiology of therapy-associated uveitis is therefore currently not known.

The primary objective of this study was to investigate if the occurrence of uveitis under treatment is more frequent than in a general population of patients without treatment for cutaneous melanoma. In secondary analyses, we investigated if the risk of uveitis differs between treatments, and if the development of uveitis was associated with systemic adverse effects during treatment with immune checkpoint or BRAF/MEK inhibitor therapy.

2. Methods

2.1. Study design and population

Data were obtained from the cancer registry of the Comprehensive Cancer Center Zurich (CCCZ), which

includes all adult patients with advanced cutaneous melanoma treated in the University Hospital of Zurich, Switzerland, since January 2008. We included all patients who had their first-line therapy of either immune checkpoint (anti-CTLA-4 or anti-PD-1 inhibitor) or BRAF/MEK inhibitors between January 2008 and December 2018. Patients with a history of uveitis, experimental treatment combinations (bevacizumab, sorafenib and selumetinib), or triple combinations of immune checkpoint and BRAF/MEK inhibitors were excluded. The analysis of the registry data was approved by the local ethics committee (KEK-ZH 2014-0193).

2.2. Outcome and independent variables

The primary outcome was the risk of non-infectious uveitis per year. We systematically searched all charts of the patients for documented ophthalmic consultations. We considered a patient having a non-infectious uveitis if the diagnosis was confirmed based on SUN criteria [27] and an ophthalmological consult in the chart has documented that possible infectious aetiologies have been ruled out. Characteristics of the patients were collected by an independent research registry team. The recorded variables included age, gender, melanoma stage, genetic pattern of melanoma, therapy with steroids, and history of uveitis, rheumatoid or infectious diseases. We considered exposure to all types of anti-CTLA-4 (ipilimumab) and/or anti-PD-1 (pembrolizumab, nivolumab) as immune checkpoint inhibitor treatment. BRAF/MEK inhibitor therapy was defined as exposure to either BRAF, MEK or BRAF/MEK inhibitor treatment. The time origin of analyses was defined as the start date of treatment. The follow-up period ended either at the occurrence of uveitis, at death, at the end of therapy (disease-progression, stop of drug intake, end of study), or at loss to follow-up.

2.3. Statistical analysis

Patient characteristics were described with proportions for categorical and mean (standard deviation) or median (interquartile range [IQR]) for continuous variables. Cumulative probability curves were computed and illustrated for the following states: occurrence of uveitis, death, or being alive. Baseline characteristics were

stratified by type of exposure to either immune checkpoint or BRAF/MEK inhibitors. No assumptions were made for missing data.

We used a Bayesian framework to answer the primary research question. A gamma prior distribution for the cumulative incidence of uveitis at 1 year in the general population was defined with a shape of 50/8 and a rate of 1/8 per 100,000 persons. The corresponding mean was defined to reflect a cumulative incidence of 50 per 100,000 person-years [28]. Markov chain Monte Carlo modelling (with 3 chains, 10,000 iterations burn-in and 50,000 saved iterations per chain) was used to derive a right-censored, exponential survival model including treatment with either immune checkpoint or BRAF/MEK inhibitor therapy as predictor variables. The model assumes a constant hazard of developing uveitis. Based on this model, we estimated the mean probability of uveitis with 95% credible intervals (CrIs) for patients treated with immune checkpoint or BRAF/MEK inhibitor therapy from the posterior distribution.

To answer the second research question, we calculated the hazard ratio to describe the difference in the hazard of developing uveitis between the two treatments. Furthermore, mean probabilities to exceed pre-specified thresholds of the hazard ratio were computed.

Three sensitivity analyses were performed. First, we restricted the data set to patients without history of rheumatological diseases and without steroid treatment. Patients with rheumatological diseases potentially have an increased baseline risk of developing uveitis, whereas steroid treatment will reduce the risk of uveitis. Second, we used a Bayesian Poisson mixture model, instead of a survival model, to confirm the robustness of our estimates for different model assumptions. Third, we repeated the analysis with a Bayesian Poisson mixture model adjusting for differences in the number of eye examinations between groups using stabilised inverse probability weights. This analysis would allow to identify detection bias due to systematic differences in terms of eye examinations between the two exposure groups. Model performance was evaluated by comparing the number of predicted cases with uveitis to observed cases with uveitis before censoring. The Gelman–Rubin statistic was used to assess model convergence.

We used 2×2 cross tabulation and the McNemar test to assess if systemic adverse effects were pairwise associated with the development of uveitis during treatment with immune checkpoint or BRAF/MEK inhibitor therapy. We considered all treatment-related adverse effects leading to hospitalisation as systemic adverse effect.

All analyses were performed in R software, version 3.5.3 (www.r-project.org), and JAGS (4.3.0) using the ‘rjags’ package [29] to run JAGS [30]. Details and the code of the analysis are available at *EJC Supplement*.

3. Results

3.1. Patients characteristics

The registry included 612 patients, of which 122 patients did not meet inclusion criteria (*eFig. 1*, available at *EJC Supplement*). A total of 490 patients were included in the final analysis. 304 patients (62%) were treated with immune checkpoint inhibitors and 186 patients (38%) with BRAF/MEK inhibitors. Eighty-two patients (16.7%) of our cohort had an ophthalmic examination. Seventy-four of these 82 patients had pre-planned eye examinations mandated by a clinical trial protocol. More ophthalmological examinations were reported in patients who were treated with BRAF/MEK compared to immune checkpoint inhibitors (68 versus 14 examinations, 36.6% versus 14.6% per group). A total of 11 patients developed uveitis (4 of 304 patients treated with immune checkpoint inhibitors and 7 of 186 patients treated with BRAF/MEK inhibitors), while 30 patients died during the treatment (*Fig. 1*). Median (IQR) time of follow-up for patients with immune checkpoint inhibitor treatment was 63 days (42–94 days) and for patients with BRAF/MEK inhibitor treatment was 172 days (94.50–332 days). Thirty-one patients (6%) had a documented history of a rheumatological disease, and 51 patients (10.4%) had a documented history of treatment with steroids at baseline. During follow-up, treatment with steroids was recorded in 149 patients (30%). The steroids were newly prescribed in 113 of 149 patients during follow-up, while a pre-existing therapy with steroids was continued in 36 patients. Sixty-two of the 149 patients treated with steroids during follow-up (42%) had brain metastasis. Eighty-two of the 149 patients treated with steroids during follow-up (55%) had systemic adverse effects of the therapy. Details of the patient's baseline characteristics are illustrated in *Table 1*.

3.2. The risk of uveitis during treatment compared to the general population

Based on previous work describing the incidence of uveitis between 17 and 52 cases per 100,000 person-years (*Table 2*), we assumed a more conservative prior probability of 0.05% (95% CrI: 0.02%–0.1%) regarding the risk of developing uveitis in the general population per year. Compared with the general population, patients with cutaneous melanoma who received immune checkpoint or BRAF/MEK inhibitor therapy had an 83-fold (95% CrI: 16–236) or 120-fold (95% CrI: 34–313) increased risk of developing uveitis. In absolute values, the probabilities of developing uveitis during a 1-year treatment were 3.48% (95% CrI: 0.93%–7.49%) and 5.04% (95% CrI: 2.07%–9.19%) for immune checkpoint or BRAF/MEK

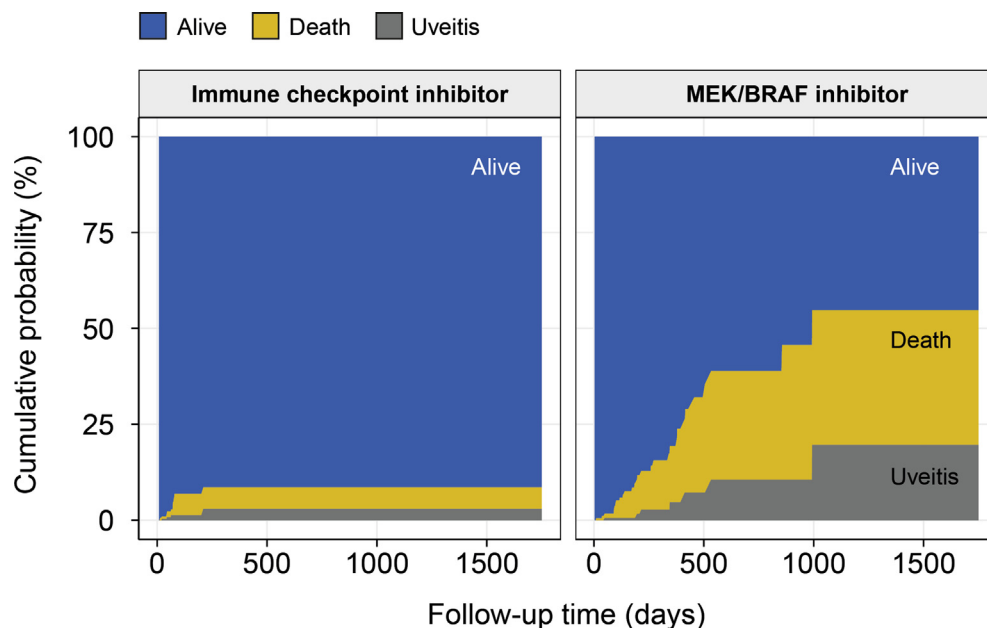


Fig. 1. **Outcome in relation to treatment regimen for advanced cutaneous melanoma.** Cumulative probability curves stratified by treatment with either immune checkpoint or BRAF/MEK inhibitors are illustrated for the following states: being alive, death or occurrence of uveitis ($n = 490$). BRAF, B-Raf proto-oncogene; MEK, mitogen-activated protein kinase.

inhibitor therapy, respectively. Systemic adverse events were not associated with the development of uveitis (McNemar's chi-squared = 120.89, $df = 1$, p -value <0.001) (eTable 1).

In a sensitivity analysis, we excluded patients with a previous history of rheumatological disease or therapy with steroids. In this subgroup analysis, the probabilities of developing uveitis were 1.40% (95% CrI: 0.06%–

Table 1
Baseline characteristics and outcomes of patients with advanced cutaneous melanoma.

Characteristic	All patients	Immune checkpoint inhibitors	BRAF/MEK inhibitors
N	490	304	186
Age, y	62 [50, 72]	64 [52, 72]	58 [49, 71]
Women, no. (%)	189 (38.6)	116 (38.2)	73 (39.2)
Rheumatological disease, no (%)	31 (6.3)	21 (6.9)	10 (5.4)
Therapy with steroids, no (%)	51 (10.4)	27 (8.9)	24 (12.9)
Melanoma disease			
BRAF+, no. (%)	254 (51.7)	89 (29.3)	165 (88.7)
NRAS+, no (%)	85 (17.3)	74 (24.3)	12 (6.5)
BRAF-/NRAS-, or not specified (%)	152 (31.0)	141 (46.4)	11 (5.9)
Metastatic sites involved ≤ 2 , no. (%)	304 (62.0)	213 (70.1)	91 (48.9)
Brain metastasis, no. (%)	103 (21.0)	43 (14.1)	60 (32.3)
Immune checkpoint inhibitors			
Anti-CTLA-4	235 (48.0)	235 (77.3)	—
Anti-PD1	98 (20.0)	98 (32.2)	—
Anti-CTLA-4/PD-1	29 (5.9)	29 (9.5)	—
BRAF/MEK inhibitors			
BRAF	109 (22.2)	—	109 (58.6)
MEK	21 (4.3)	—	21 (11.3)
BRAF/MEK	56 (11.4)	—	56 (30.1)
Ophthalmological examination, no. (%)	82 (16.7)	14 (4.6)	68 (36.6)
Outcomes			
Alive, no. (%)	449 (91.6)	292 (96.1)	157 (84.4)
Uveitis, no. (%)	11 (2.2)	4 (1.3)	7 (3.8)
Death, no. (%)	30 (6.1)	8 (2.6)	22 (11.8)
Follow-up time, d	74 [57,233]	63.00 [42, 94]	172 [95, 332]

We considered exposure to all types of anti-CTLA-4 (ipilimumab) or anti-PD1 (pembrolizumab, nivolumab) as immune checkpoint inhibitor treatment. BRAF/MEK inhibitor therapy was defined as exposure to either BRAF, MEK or BRAF/MEK combination inhibitor treatment. MEK, Mitogen-activated protein kinase; BRAF, B-Raf proto-oncogene.

Table 2
Reported incidence of uveitis in different population-based studies.

Author	Region	Population size	Incidence of uveitis (per 100 000 person-years)
Acharya 2013 [33]	California and Hawaii, United States	217,061	24.9
Gritz 2004 [28]	California, United States	731,895	52
Saari 1995 [34]	Finland	459,515	22.6
Tran 1994 [35]	Switzerland	558	17.5

5.06%) and 2.16% (95% CrI: 0.27%–6.00%) for immune checkpoint or BRAF/MEK inhibitors. The robustness of our estimates was confirmed in an analysis using a Bayesian mixture model (see supplementary information available at [EJC Supplement](#)).

3.3. Difference in risks of uveitis between immune checkpoint and BRAF/MEK inhibitor therapy

Patients under treatment with BRAF/MEK inhibitors had a two-fold higher hazard of developing uveitis (hazard ratio: 2.00; 95% CrI: 0.43–6.32). The probability that patients with BRAF/MEK inhibitor therapy have a higher risk of developing uveitis was 75.9% ([eTable 2](#) available at [EJC Supplement](#)). The probability for an increase of >40% in the hazard of developing uveitis was 57.5%. Similar results were found in a sensitivity analysis using inverse probability weighting to adjust for different number of eye exams between exposure groups ([eTable 3](#) available at [EJC Supplement](#)). All four cases of uveitis (1.3%) in patients treated with immune checkpoint inhibitors were observed under treatment with anti-CTLA-4 inhibitors. No uveitis was detected in patients treated with anti-PD-1 inhibitors.

3.4. Characteristics of treatment-related uveitis

In eight of 11 patients with uveitis, eye symptoms led to a referral to the ophthalmologist. Three uveitis cases were diagnosed during a scheduled ophthalmic examination mandated as part of a clinical trial protocol. Two of the three patients were completely asymptomatic. Most patients with uveitis presented with a bilateral, anterior fibrinous uveitis with small keratic precipitates and a tendency to progress with posterior synechiae and vitreous spill over. Clinical findings (slit lamp and biomicroscopy) were similar in patients treated with immune checkpoint and BRAF/MEK inhibitor therapy.

Recurrence of uveitis was frequent, and complications requiring systemic steroids in 4/11 included macular oedema, papilloedema, elevated intraocular pressure, late formation of cataract, or development of epiretinal membranes ([Fig. 2](#)). Persistent reduction of visual acuity was observed in five of 11 patients. No one had to discontinue the oncological therapy. Additional details are presented in [Table 3](#).

4. Discussion

Immune checkpoint and particularly BRAF/MEK inhibitor therapy were associated with a significant increase in the risk of uveitis compared with the general population. While in our cohort, the mean relative increase in the risk of uveitis was between 80- and 120-fold, the absolute risk can still be considered relatively low. The mean probability of developing uveitis during 1 year of treatment was between 3% and 5%. This must be interpreted in the context of a life-saving cancer therapy, which prolongs the overall survival from advanced cutaneous melanoma and other metastatic malignancies.

Our results are in good agreement with previous work on treatment-related ocular toxicities. Choe et al. reported the incidence of uveitis at 4.0% (95% CI: 2.6%–6.0%) during treatment of 568 patients with Vemurafenib for a duration ranging from 7 to 550 days [18]. Bitton et al. estimated the probability of developing a moderate to severe ocular adverse event during a 1-year treatment with anti-PD-(L)1 at 0.8% [15]. Both studies, however, did not describe if patients were treated with either immune checkpoint or BRAF/MEK inhibitors before enrollment. Alves et al. did a systematic review and meta-analysis of patients treated with MEK inhibitors but did not find an increased risk of uveitis [20]. Previous case reports described various clinical patterns of treatment-related uveitis, including the occurrence of extraocular manifestations resembling the Vogt–Koyanagi–Harada disease [22,23,25]. In our cohort, however, the development of uveitis was not associated with other systemic adverse events or extraocular toxicities.

As a strength of our work, we quantified the risk of treatment-related uveitis compared to the risk of the general population and demonstrated that the risk of uveitis is higher during first-line treatment with BRAF/MEK compared with immune checkpoint inhibitors. Interestingly, all cases of uveitis in patients treated with immune checkpoint inhibitors were observed under treatment with anti-CTLA-4 inhibitors (ipilimumab), whereas no uveitis was detected in patients solely treated with anti-PD-1 inhibitors. Our research questions could not have been answered with a traditional frequentist statistics framework. The Bayesian approach facilitated reliable estimations even with a very small number of



Fig. 2. **Epiretinal membrane on treatment with combined BRAF and MEK inhibition (encorafenib/binimetinib), a late complication of re-lapsing uveitis.** Multicolour scanning laser ophthalmoscopy and linear optical coherence tomography scan of the right eye shows the widespread yellowish epiretinal membrane, delineated as a highly reflective contour on the inner retinal surface. The central retina is stretched with abnormal foveal depression (A). In contrast, the subfoveal neuroretinal detachment (yellow arrow) is a toxic side-effect caused by the intake of an MEK inhibitor 2 h before the examination. This is emphasised by mild oedema of the outer layers in the left eye (B). Visual acuity on the right side was 20/25 and on the left side was 20/16. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

events and a limited sample size [26,31]. We used two different Bayesian modelling strategies to estimate the risk of uveitis per year and found similar estimates in the exponential survival model and in the Poisson mixture model (see supplementary information). Nevertheless, our study has several limitations. First, our analysis does not definitely prove causality. We cannot rule out that common genetic factors or immunologic phenomena related to the melanoma influence the risk for developing uveitis. As numerous other treatments besides immune checkpoint and BRAF/MEK inhibitors are known to promote the development of uveitis [32], estimation of the uveitis risk in the melanoma population is difficult.

Second, our analysis might be influenced by residual confounding. We did a sensitivity analysis restricted to patients without rheumatologic diseases and without steroid therapy to estimate the influence of confounding factors. Furthermore, information bias was minimised

by manually verifying each ophthalmologic consult of the patients in the registry.

Third, not all patients underwent regularly scheduled ophthalmologic controls during follow-up, which includes the possibility that cases of very mild, asymptomatic uveitis could have been missed. Furthermore, differences in the number of eye examinations between exposure groups could have introduced potential detection bias. However, significant under-detection of uveitis is very unlikely in a cohort of melanoma patients who were closely monitored because of their melanoma treatment. The estimates of our sensitivity analysis using inverse probability weighting to adjust for differences in the number of eye examinations between exposure groups were comparable to the estimates of the main analysis. In addition, a failure to detect mild, asymptomatic cases of uveitis would lead to more conservative estimates in our analysis.

Table 3
Characteristics of uveitis during immune checkpoint or BRAF/MEK inhibitor therapy.

Case	Age (Sex)	First-line oncologic treatment	Time to uveitis (days)	Symptoms (CTCAE grade)	Systemic adverse events	Location	Onset/Duration/Course	Grade/Findings	Outcome of melanoma
1	33 (M)	Anti-CTLA4	52	Blurred vision, floaters myopisation (3)	Colitis	Anterior + intermediate	Insidious, persistent, chronic	3+/3+; Posterior synechiae, elevated io pressure, vitreous haze, floaters, retinal + papilloedema	PD
2	43 (M)	BRAF ⁱ + MEK ⁱ	533	Red eye, irritation (2)	Sarcoid-like immune reaction	Anterior	Sudden, limited, recurrent	2+/1+; Posterior synechiae, later epiretinal membrane	PR
3	55 (M)	Anti-CTLA4 + Anti-PD1	154	No symptoms (1)	Colitis Vitiligo	Anterior + intermediate + retina	Insidious, persistent, recurrent	2+/2+; Vitreous haze + cells cystoid retinal oedema, epiretinal membrane	SD
4	82 (F)	BRAF ⁱ + MEK ⁱ	345	Red eye, irritation (2)	None	Anterior + intermediate	Sudden, limited, acute	4+/4+, Hypotonia, serous retinal detachment	PD
5	77 (M)	BRAF ⁱ + MEK ⁱ	196	No symptoms (1)	None	Anterior + intermediate + optic nerve	Insidious, limited, acute	2+/2+; Posterior synechiae; vitreous haze, retinal bleeding, papilloedema	PD
6	58 (M)	BRAF ⁱ	141	Blurred vision, red eye (2)	None	Anterior + intermediate	Insidious, persistent, recurrent	2+/2+; Posterior synechiae	PD
7	50 (F)	BRAF ⁱ	47	Blurred vision (2)	None	Anterior + intermediate + retina	Sudden, recurrent	Posterior synechiae, retinal vasculitis	PD
8	37 (F)	BRAF ⁱ + MEK ⁱ	628	Blurred vision (2)	None	Anterior + intermediate + macula	Sudden, chronic	2+/2+; Posterior synechiae; macular oedema	PD
9	73 (F)	Anti-CTLA4 + Anti-PD1	62	ns	None	Anterior, bilateral	ns	Posterior synechiae, uveal melanoma left	PD
10	73 (M)	BRAF ⁱ	60	ns	None	Anterior	ns	ns	PD
11	43 (M)	Anti-CTLA4	45	Blurred vision (3)	CRS	Anterior + intermediate + optic nerve	Sudden, persistent	2+/2, Elevated io pressure, papilloedema	PD

The severity of symptoms was graded using the classification of the CTCAEv4. The type and severity of uveitis was graded according to SUN criteria [27].

CRS, Cytokine release syndrome; CR, complete response; SD, stable disease; PR, partial response; PD, progressive disease; ns, not specified; CTCAE, Common Terminology Criteria for Adverse Events; SUN, standardisation of uveitis nomenclature.

Fourth, our analysis does not answer the question whether a triple combination therapy (BRAF/MEK/PD1 inhibitors) additionally increases the risk of uveitis. Our registry only comprised three patients on triple therapy. Reliable estimation of an interaction term was therefore not feasible.

Finally, uveitis is considered an orphan disease showing large geographic and ethnic differences. Therefore, the prior gamma distribution with a mean incidence rate of 50 per 100,000 person-years might be at the upper limit of the true incidence rate in Switzerland (Table 2). Also, the duration of follow-up in our study is relatively short for the detection of uveitis. Both factors could have resulted in more conservative estimates of our analysis.

The novel treatment strategies have resulted in a prolonged overall survival of cancer patients. Furthermore, combination or sequenced therapies are currently investigated, which will likely result in an increased rate of treatment-related uveitis and in more late complications. Further research is needed to investigate whether uveitis represents a surrogate marker for mortality. Patients must be informed about the risk of uveitis before initiation of therapy. Considering the significantly increased risk of developing treatment-related uveitis during immune checkpoint and BRAF/MEK inhibitor therapy, an immediate referral and interdisciplinary approach is required in patients with eye symptoms to allow early intervention and prevention of serious functional loss.

Author contributions

Study concepts: FD, UU, JM, RD, MU; Study design: FD, UU, JM, RD, MU; Data acquisition: FD, UU, JM, CE; Quality control of data and algorithms: FD, UU, JM, CE; Data analysis and interpretation: UU, NM, MU; Statistical analysis: NM, MU; Manuscript preparation: FD, UU, MU; Manuscript editing: FD, UU, JM, RD, CE, MU; Manuscript review: FD, UU, JM, RD, CE, NM, MU.

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Conflict of interest statement

FD receives intermittent travel support from Amgen and Pierre Fabre outside of the submitted work. JM has intermittent project focused consultant or advisory relationships with Merck/Pfizer, Merck Sharp & Dohme and Pierre Fabre and has received travel support from Ultrasun, L'Oréal, Merck Sharp & Dohme, Bristol-

Myers Squibb (BMS) and Pierre Fabre outside of the submitted work. RD has intermittent, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi outside the submitted work. MU is supported by a Vanier Canada Graduate Scholarship from the Canadian Institutes of Health Research. CE, NM and UU declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2020.11.027>.

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